Pergamon

Appl. Math. Lett. Vol. 9, No. 4, pp. 35–40, 1996

0893-9659/96 $15.00 + 0.00

S0893-9659(96)00048-1

Membrane Diffusion and Flux Response

M. SUZUKI
Department of Mathematics, The University of Queensland
Brisbane, QLD 4072, Australia

A. MCNABB
Department of Mathematics, Division of Science and Technology
The University of Auckland, Auckland, New Zealand

A. J. BRACKEN
Department of Mathematics, The University of Queensland
Brisbane, QLD 4072, Australia

(Received December 1995; accepted January 1996)

Abstract—A linear diffusion convection equation for the transport of a single chemical component through a membrane is coupled with a linear reaction equation describing interaction of the diffusing chemical with an immobile reactant. Expressions are derived for the flux responses in and out of the membrane to given concentrations applied at one side of the membrane while zero concentration is maintained at the other. These fluxes are compared with the corresponding fluxes for the complementary experiment in which the imposed boundary concentration at the two faces of the membrane are interchanged. Ussing-type flux-ratio relationships are obtained for the outflow fluxes, but the inflow fluxes respond in a different way, and it is found that the difference of the influxes for complementary experiments remain constant for all time.

Keywords—Diffusion, Flux, Flux ratio, Accumulated flux.

1. INTRODUCTION

Studies of chemical transport through biological membranes often involve measurements of chemical fluxes responding to imposed chemical concentrations on one side of a membrane. The Danish physiologist Ussing pioneered a technique for investigating membrane transport kinetics by comparing fluxes from reciprocal experiments in which the imposed boundary concentrations are transposed to opposite sides of the membrane [1]. His analysis of diffusion-convection models of the transport considered systems starting from zero concentration, with zero concentration maintained on one side and a constant concentration on the other. Such boundary conditions were found to generate a flux out of the zero-concentration boundary, which was in many cases in a constant ratio to the corresponding flux for the reciprocal experiment. The deviation of this ratio from unity is a measure of the asymmetry of the transport equations and indicates the presence of a potential gradient driving convection and enhancing the flux in one direction. The constancy of this ratio for all times, even in the presence of such asymmetries, is quite counterintuitive but has now been demonstrated theoretically for a large class of models [2–5].

These fascinating results have tended to focus attention on just one half of the membrane response to the imposed boundary and initial concentrations, the outfluxes at the zero-concentration

This research project was partially supported by the New Zealand Foundation for Research, Science and Technology under a grant from the Marsden Fund.

Typeset by $\mathcal{A}_\mathcal{M}\mathcal{S}$-TEX boundary. In this note, we examine the influxes at the opposite boundary. For linear one-dimensional membrane models with constant diffusivity, constant convective velocity and constant trapping parameters for the transport of a single chemical, we find an influx result for reciprocal experiments similar to that of Ussing, but involving the flux difference instead of the ratio. It is shown that the difference between the influxes for the reciprocal experiments is constant for all time and gives a measure of the driving potential augmenting the diffusion.

The transport model equations in one-dimensional form are formulated in nondimensional form in Section 2 and solved using Laplace transform techniques for the fluxes into and out of the membrane for pairs of complementary experiments in Section 3. Analogous expressions are derived in Section 4 for accumulated fluxes and their asymptotic long time behaviour. When the boundary conditions are constant, the linear asymptotes for the outfluxes for complementary experiments are found to intersect on the time axis, while the corresponding asymptotes for the influxes are found to intersect on the accumulating flux axis.

2. TRANSPORT EQUATIONS

The diffusion-reaction equations considered here form a linear system with constant coefficients describing diffusion with trapping on an interval $(0, L)$. A concentration $c(x,t)$ of a chemical component is trapped and immobilized as another phase or component at a concentration $w(x,t)$. The flux $j(x,t)$ of $c(x,t)$ is governed by a fixed diffusivity D and potential v, while the trapping kinetics are described by constant binding and release coefficients k^* and λ^*, so that the concentrations $c(x,t)$ and $w(x,t)$ are solutions of the system of equations

$$\frac{\partial c(x,t)}{\partial t} + \frac{\partial j(x,t)}{\partial x} = -\frac{\partial w(x,t)}{\partial t}, \tag{1}$$

$$j(x,t) = -D\,\frac{\partial c(x,t)}{\partial x} + vc(x,t), \qquad 0 < x < L, \quad t \geq 0, \tag{2}$$

$$\frac{\partial w(x,t)}{\partial t} = k^* c - \lambda^* w. \tag{3}$$

The symmetry of these equations under reflection about $x = L/2$ is broken only by the convection term with constant coefficient v; when in addition the sign of v is reversed, the equations are unchanged.

The differential equations (1)–(3) for $c(x,t)$, $w(x,t)$ and flux $j(x,t)$ subject to initial conditions $c(x,0) = w(x,0) = 0$, and prescribed boundary conditions $c(0,t)$ and $c(L,t)$, can be expressed in the dimensionless forms

$$\frac{\partial C(\chi,\tau)}{\partial \tau} + \frac{\partial J(\chi,\tau)}{\partial \chi} = -\frac{\partial W(\chi,\tau)}{\partial \tau}, \tag{4}$$

$$J(\chi,\tau) = -\frac{\partial C(\chi,\tau)}{\partial \chi} + \beta C(\chi,\tau), \qquad 0 < \chi < 1, \quad \tau \geq 0, \tag{5}$$

$$\frac{\partial W(\chi,\tau)}{\partial \tau} = kC(\chi,\tau) - \lambda W(\chi,\tau), \tag{6}$$

where the nondimensional parameters are

$$\tau = \frac{D}{L^2}t, \qquad \chi = \frac{x}{L}, \qquad \beta = \frac{vL}{D}, \qquad \lambda = \frac{L^2}{D}\lambda^*, \qquad k = \frac{L^2}{D}k^*,$$

$$c(\chi,\tau) = c_0 C(x,t), \qquad w(\chi,\tau) = c_0 W(x,t), \qquad J(\chi,\tau) = \frac{L}{Dc_0} j(x,t),$$

so that $C(\chi,0) = 0$, $C(0,\tau) = c(0,t)/c_0 \equiv f(\tau)$ and $C(1,\tau) = c(L,t)/c_0 \equiv g(\tau)$.

We need only solve this system for the case $f(\tau) = 0$ and $g(\tau)$ arbitrary, since the complementary problem for which $g(t) = 0$, defining C^* and W^*, is obtained from this by changing the sign of β. The sum of these cases gives the solution of the problem with general boundary conditions.

3. FLUX RESPONSE OF SYSTEMS

The steady-state concentration C^{ss} corresponding to $f(\tau) = 0$ and $g(\tau) = 1$, and approached as τ tends to infinity, together with the steady-state fluxes J_{in}^{ss}, J_{out}^{ss} in through $\chi = 1$ and out through $\chi = 0$, are given by

$$C_{\text{in}}^{ss} = \frac{\beta}{e^{\beta} - 1}, \qquad J_{\text{in}}^{ss} = J_{\text{out}}^{ss} = \frac{e^{\beta\chi} - 1}{e^{\beta} - 1}. \tag{7}$$

The general time-dependent problem readily yields to Laplace transform techniques and

$$\bar{C}(\chi, p) = \int_0^\infty e^{(-p\tau)} C(\chi, \tau)\, d\tau, \qquad \bar{J}(\chi, p) = \int_0^\infty e^{(-p\tau)} J(\chi, \tau)\, d\tau \tag{8}$$

satisfy the equations

$$\frac{\partial^2 \bar{C}(\chi, p)}{\partial \chi^2} - \beta \frac{\partial \bar{C}(\chi, p)}{\partial \chi} - \frac{p(p + \lambda + k)}{p + \lambda} \bar{C}(\chi, p) = 0, \tag{9}$$

$$\bar{J}(\chi, p) = -\frac{\partial \bar{C}}{\partial \chi} + \beta \bar{C}(\chi, p), \tag{10}$$

$$\bar{C}(0, p) = \bar{f}(p), \qquad \bar{C}(1, p) = \bar{g}(p). \tag{11}$$

It follows that $\bar{C}(\chi, p) = A_1 e^{\mu_1 \chi} + A_2 e^{\mu_2 \chi}$, where μ_i are the roots of

$$\mu^2 - \beta\mu - \frac{p(p + \lambda + k)}{p + \lambda} = 0. \tag{12}$$

The boundary conditions

$$\bar{C}(0, p) = \bar{f}(p) = A_1 + A_2, \qquad \bar{C}(1, p) = \bar{g}(p) = A_1 e^{-\mu_1} + A_2 e^{-\mu_2}, \tag{13}$$

lead to the following expressions for A_i and $\bar{C}(\chi, p)$:

$$A_1 = \frac{\bar{f} e^{\mu_2} - \bar{g}}{(e^{\mu_2} - e^{\mu_1})}, \qquad A_2 = \frac{\bar{g} - \bar{f} e^{\mu_1}}{(e^{\mu_2} - e^{\mu_1})}, \tag{14}$$

$$\bar{C}(\chi, p) = \frac{\left(\bar{f} e^{\mu_2} - \bar{g}\right) e^{\mu_1 \chi} - \left(\bar{f} e^{\mu_1} - \bar{g}\right) e^{\mu_2 \chi}}{(e^{\mu_2} - e^{\mu_1})}, \tag{15}$$

and the flux transform

$$\bar{J}(\chi, \tau) = -\frac{\left(\bar{f} e^{\mu_2} - \bar{g}\right) \mu_1 e^{\mu_1 \chi} - \left(\bar{f} e^{\mu_1} - \bar{g}\right) \mu_2 e^{\mu_2 \chi}}{(e^{\mu_2} - e^{\mu_1})} + \beta \frac{\left(\bar{f} e^{\mu_2} - \bar{g}\right) e^{\mu_1 \chi} - \left(\bar{f} e^{\mu_1} - \bar{g}\right) e^{\mu_2 \chi}}{(e^{\mu_2} - e^{\mu_1})}. \tag{16}$$

This leads to the boundary flux expressions

$$\bar{J}(0, \tau) = \frac{\left(\bar{f} e^{\mu_2} - \bar{g}\right)(\beta - \mu_1) - \left(\bar{f} e^{\mu_1} - \bar{g}\right)(\beta - \mu_2)}{(e^{\mu_2} - e^{\mu_1})}, \tag{17}$$

$$\bar{J}(1, \tau) = \frac{\left(\bar{f} e^{\beta} - \bar{g} e^{\mu_1}\right)(\beta - \mu_1) - \left(\bar{f} e^{\beta} - \bar{g} e^{\mu_2}\right)(\beta - \mu_2)}{(e^{\mu_2} - e^{\mu_1})}. \tag{18}$$

Consider the case $f = 0$, and compare the fluxes in at $\chi = 1$ and out at $\chi = 0$ with the corresponding fluxes for the complementary solution for which the sign of β is reversed. It can be seen that the roots μ^* for the complementary case are given by $\mu_i = \mu_i^* + \beta$, and so we have

$$\bar{J}_{\text{in}} = -\bar{J}(1, p) = \frac{\bar{g}\left[e^{\mu_1}(\beta - \mu_1) - e^{\mu_2}(\beta - \mu_2)\right]}{(e^{\mu_2} - e^{\mu_1})}, \qquad \bar{J}_{\text{out}} = -\bar{J}(0, p) = \frac{\bar{g}(\mu_2 - \mu_1)}{(e^{\mu_2} - e^{\mu_1})}, \tag{19}$$

$$\bar{J}_{\text{in}}^* = -\bar{J}^*(1, p) = \frac{\bar{g}\left[e^{\mu_1}(-\mu_1) - e^{\mu_2}(-\mu_2)\right]}{(e^{\mu_2} - e^{\mu_1})}, \qquad \bar{J}_{\text{out}}^* = -\bar{J}^*(0, p) = \frac{\bar{g}(\mu_2 - \mu_1)e^{-\beta}}{(e^{\mu_2} - e^{\mu_1})}. \tag{20}$$

The pair of output flux expressions give the Ussing flux ratio result

$$\bar{J}^*_{\text{out}} = \bar{J}_{\text{out}} e^{-\beta} \qquad \text{so that } J^*_{\text{out}}(\tau) = J_{\text{out}}(\tau) e^{-\beta}, \tag{21}$$

while the pair of inflow flux expressions gives an equally simple relationship

$$\bar{J}_{\text{in}} - \bar{J}^*_{\text{in}} = -\beta\bar{g} \quad \text{or} \quad J_{\text{in}}(\tau) - J^*_{\text{in}}(\tau) = -\beta g(\tau). \tag{22}$$

The Ussing result obtained here for the outfluxes has been shown to hold in much more general circumstances [1–5]. The diffusivity D and the velocity term v may both be be functions of x, and the geometry may be N-dimensional. Such extensions are unlikely to hold for influxes, since the initial behavior is governed predominantly by the geometry and physical properties of the medium near the input boundary.

4. ACCUMULATED FLUXES

The amounts $Q_{\text{in}}(\tau)$, $Q_{\text{out}}(\tau)$ of diffusate which pass into and out of the membrane in time τ in the case that $f = 0$, and the corresponding quantities for the complementary experiment, are given by the expressions

$$Q_{\text{out}}(\tau) = \int_0^\tau J_{\text{out}}(s)\,ds, \qquad Q^*_{\text{out}}(\tau) = \int_0^\tau J^*_{\text{out}}(s)\,ds, \tag{23}$$

$$Q_{\text{in}}(\tau) = \int_0^\tau J_{\text{in}}(s)\,ds, \qquad Q^*_{\text{in}}(\tau) = \int_0^\tau J^*_{\text{in}}(s)\,ds, \tag{24}$$

so that

$$Q_{\text{out}}(\tau) = e^{\beta} Q^*_{\text{out}}(\tau) \tag{25}$$

$$Q_{\text{in}}(\tau) - Q^*_{\text{in}}(\tau) = -\beta \int_0^\tau g(s)\,ds. \tag{26}$$

In cases where the integral of $g(\tau)$ converges as $t \to \infty$, for example when g is a step function, these formulae define the total amount of chemical in and out of the membrane during the experiment. Thus,

$$Q_{\text{out}}(\infty) = e^{\beta} Q^*_{\text{out}}(\infty), \qquad Q_{\text{in}}(\infty) - Q^*_{\text{in}}(\infty) = -\beta \int_0^\infty g(s)\,ds. \tag{27}$$

These results have a more general setting. We see from (4)–(6) that

$$\int_0^\tau \left[\frac{\partial C(\chi,s)}{\partial s} + \frac{\partial W(\chi,s)}{\partial s} + \frac{\partial J(\chi,\tau)}{\partial \chi}\right] d\tau = C(\chi,\tau) + W(\chi,\tau) + \frac{\partial}{\partial\chi}\int_0^\tau J(\chi,s)\,ds = 0, \tag{28}$$

$$\int_0^\tau J(\chi,s)\,ds = -\frac{\partial\theta}{\partial\chi}(\chi,\tau) + \beta\theta(\chi,\tau), \tag{29}$$

where $\theta(\chi,\tau) = \int_0^\tau C(\chi,s)\,ds$. Since $g(\tau) \to 0$ as $\tau \to \infty$ if its integral is to converge, then $C(\chi,\tau)$ and $W(\chi,\tau)$ also decay to zero as $\tau \to \infty$, and then it follows from (28),(29) that

$$\frac{\partial}{\partial\chi}\int_0^\infty J(\chi,\tau)\,d\tau = -\frac{\partial^2\theta}{\partial\chi^2}(\chi) + \beta\frac{\partial\theta}{\partial\chi}(\chi) = 0, \tag{30}$$

$$\theta(0) = 0, \qquad \theta(1) = I = \int_0^\infty g(s)\,ds, \tag{31}$$

where $\theta(\chi) = \theta(\chi, \infty) = \int_0^\infty C(\chi, s)\, ds$. Note that (30),(31) still hold if the trapping reaction is nonlinear with the general form

$$\frac{\partial W}{\partial \tau} = F(C, W), \tag{32}$$

provided (as expected on physical grounds) $C(\chi,\tau)$ and $W(\chi,\tau)$ still go to zero as $\tau \to \infty$, and this generalization preserves the invariance of the system under reversal of the sign of both $1/2-\chi$ and β. In this case, we see from (28),(29) by integrating with respect to χ from zero to one that

$$Q_{\text{in}}(\infty) = Q_{\text{out}}(\infty) = e^{\beta} Q^*_{\text{out}}(\infty) = e^{\beta} Q^*_{\text{in}}(\infty). \tag{33}$$

Moreover,

$$\begin{gathered}\int_0^\infty J(\chi,\tau)\, d\tau = -\frac{\partial \theta}{\partial \chi}(\chi) + \beta\theta(\chi) = -e^{\beta\chi}\frac{\partial}{\partial \chi}\left[e^{-\beta\chi}\theta(\chi)\right] = K, \\ \theta(0) = 0, \qquad \theta(1) = I = \int_0^\infty g(s)\, ds\end{gathered} \tag{34}$$

where K is a constant given by $K = \beta I/(1-e^{\beta})$ since $\theta(\chi) = K(1-e^{\beta\chi})/\beta$ and $\theta(1) = I$. Thus,

$$Q_{\text{in}}(\infty) = \int_0^\infty J(1,\tau)\, d\tau = K = \frac{\beta I}{1-e^{\beta}}, \qquad Q^*_{\text{in}}(\infty) = -\frac{\beta I}{1-e^{-\beta}}, \tag{35}$$

$$Q_{\text{in}}(\infty) - Q^*_{\text{in}}(\infty) = \frac{\beta I}{1-e^{\beta}} - \frac{-\beta I}{1-e^{-\beta}} = \beta I. \tag{36}$$

A similar result may be obtained for the case where v is constant, while D is x-dependent but symmetric about $\chi = 1/2$.

In cases where $g(\tau)$ tends to a nonzero constant g_∞ as $\tau \to \infty$, equations (23)–(25) give the asymptotic behavior for $Q_{\text{out}}(\tau)$ for large time

$$Q_{\text{out}}(\tau) = \int_0^\tau J_{\text{out}}(s)\, ds = J^{\text{ss}}_{\text{out}}\,\tau - \int_0^\tau \left[J^{\text{ss}}_{\text{out}} - J_{\text{out}}(s)\right] ds \sim J^{\text{ss}}_{\text{out}}(\tau - \tau_L), \tag{37}$$

where

$$J^{\text{ss}}_{\text{out}}\,\tau_L = \int_0^\infty \left[J^{\text{ss}}_{\text{out}} - J_{\text{out}}(s)\right] ds, \tag{38}$$

defining τ_L, which we shall call the output time-lag for this problem. The output time-lag for the complementary problem is given by

$$J^{*\,\text{ss}}_{\text{out}}\tau^*_L = \int_0^\infty \left[J^{*\,\text{ss}}_{\text{out}} - J^*_{\text{out}}(s)\right] ds, \tag{39}$$

so that from (21),

$$J^{\text{ss}}_{\text{out}}\tau^*_L = \int_0^\infty \left[J^{\text{ss}}_{\text{out}} - J_{\text{out}}(s)\right] ds. \tag{40}$$

Therefore, $\tau^*_L = \tau_L$, and as (37) shows, when $Q_{\text{out}}(\tau)$ and $Q^*_{\text{out}}(\tau)$ are plotted against τ, their asymptotes for large τ will intersect on the τ-axis at their common output time-lag $\tau = \tau_L = \tau^*_L$.

On the other hand, the asymptotes for the inflow problems are given by similar expressions and equations for the time-lags, and we see from (24) that

$$Q_{\text{in}}(\tau) - Q^*_{\text{in}}(\tau) = \left[J^{\text{ss}}_{\text{in}} - J^{*\,\text{ss}}_{\text{in}}\right]\tau - \int_0^\tau \left[J^{\text{ss}}_{\text{in}} - J_{\text{in}}(s)\right] ds + \int_0^\tau \left[J^{*\,\text{ss}}_{\text{in}} - J^*_{\text{in}}(s)\right] ds \tag{41}$$

$$= \beta g_\infty \tau - \beta \int_0^\tau \left[g_\infty - g(s)\right] ds. \tag{42}$$

The intercepts $Q_{\text{in},0}$ and $Q^*_{\text{in},0}$ of these asymptotes with the Q-axis at $\tau = 0$, given by

$$Q_{\text{in},0} = J^{\text{ss}}_{\text{in}} \tau_{\text{in},L}, \qquad Q_{\text{in},0} = J^{*\,\text{ss}}_{\text{in}} \tau^*_{\text{in},L}, \tag{43}$$

satisfy

$$Q_{\text{in},0} - Q^*_{\text{in},0} = J^{\text{ss}}_{\text{in}} \tau_{\text{in},L} - J^{*\,\text{ss}}_{\text{in}} \tau^*_{\text{in},L} = \beta \int_0^\infty [g(s) - g_\infty]\, ds. \tag{44}$$

For constant g, these asymptotes intersect on the Q-axis. Formulae can be obtained for these time-lags from the Laplace transforms of the fluxes. Thus,

$$\int_0^\infty e^{-p\tau} \left[J^{\text{ss}}_{\text{in}} - J_{\text{in}}(1,\tau)\right] d\tau = \frac{J^{\text{ss}}_{\text{in}}}{p} + \frac{\bar{g}\left[e^{\mu_1}(\beta - \mu_1) - e^{\mu_2}(\beta - \mu_2)\right]}{e^{\mu_2} - e^{\mu_1}}, \tag{45}$$

and if the limit as p tends to zero exists, it gives $J^{\text{ss}}_{\text{in}} \tau_L$, where τ_L is the time-lag.

Expanding to the first-order terms in p gives

$$\int_0^\infty e^{-p\tau} \left[J^{\text{ss}}_{\text{in}} - J_{\text{in}}(1,\tau)\right] d\tau = J^{\text{ss}}_{\text{in}} \left\{\frac{1}{p} - \bar{g} + \frac{\bar{g} p \alpha}{\beta}\left[\frac{2e^\beta}{e^\beta - 1} - \frac{e^\beta + 1}{\beta}\right]\right\}, \tag{46}$$

where $\alpha = (1 + \lambda/k)$ and so as p goes to zero, we get

$$\tau_{\text{in},L} = \left\{\int_0^\infty \left[1 - \frac{g(s)}{g_\infty}\right] ds + \frac{\alpha}{\beta}\left[\frac{2e^\beta}{e^\beta - 1} - \frac{e^\beta + 1}{\beta}\right]\right\}. \tag{47}$$

The corresponding expression for the output time-lag is

$$\tau_{\text{out},L} = \left\{\int_0^\infty \left[1 - \frac{g(s)}{g_\infty}\right] ds + \frac{\alpha}{\beta}\left[\frac{e^\beta + 1}{e^\beta - 1} - \frac{2}{\beta}\right]\right\}. \tag{48}$$

5. CONCLUSIONS

The information gleaned from complementary membrane flux expressions could be enhanced by examining the influxes as well as the outfluxes of diffusate. The outfluxes appear to present a global perspective on the transport asymmetries which does not change with time. On the other hand, the influxes initially respond to the local properties in the neighborhood of the input boundaries, and as time progresses their behavior becomes modified by medium properties over larger regions eventually encompassing the whole domain.

REFERENCES

1. H.H. Ussing, Interpretation of tracer fluxes, In *Membrane Transport in Biology*, Volume 1, (Edited by G. Giebisch, D.C. Tosteson and H.H. Ussing), pp. 115–140, Springer, New York, (1978).
2. L. Bass and A.J. Bracken, The flux-ratio equation under nonstationary boundary conditions, *Mathematical Biosciences* **66**, 87–92 (1983).
3. L. Bass, A.J. Bracken and J. Hilden, Flux ratio theorems for nonstationary membrane transport with temporary capture of tracer, *Journal of Theoretical Biology* **118**, 327–338 (1986).
4. O. Sten-Knudsen and H.H. Ussing, The flux ratio equation under nonstationary conditions, *Journal of Membrane Biology* **63**, 233–242 (1981).
5. A.J. Bracken, K. Holmaker, L.V. Maloney and L. Bass, Flux ratios for biological membranes and reciprocal theorems for linear operators, *Journal of Australian Mathematical Society* **B-30**, 278–297 (1989).